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AMENDMENTS TO THE SPECIFICATION

1. Please add the following paragraphs after page 11, line 12

Polymeric materials which are capable of forming a hydrogel may be utilized. In one embodiment, the polymer forms a hydrogel within the body upon contact with a crosslinking agent. A hydrogel is defined as a substance formed when an organic polymer (natural or synthetic) is crosslinked via covalent, ionic, or hydrogen bonds to create a three-dimensional open-lattice structure which entraps water molecules to form a gel. Naturally occurring and synthetic hydrogel forming polymers, polymer mixtures and copolymers may be utilized as hydrogel precursors.

Examples of materials which can be used to form a hydrogel include modified alginates. Alginate is a carbohydrate polymer isolated from seaweed, which can be crosslinked to form a hydrogel by exposure to a divalent cation such as calcium, as described, for example in WO 94/25080. Alginate is ionically crosslinked in the presence of divalent cations, in water, at room temperature, to form a hydrogel matrix. Modified alginate derivatives may be synthesized which have an improved ability to form hydrogels. The use of alginate as the starting material is advantageous because it is available from more than one source, and is available in good purity and characterization. As used herein, the term "modified alginates" refers to chemically modified alginates with modified hydrogel properties. Naturally occurring alginate may be chemical modified to produce alginate polymer derivatives that degrade more quickly. For example, alginate may be chemically cleaved to produce smaller blocks of gellable oligosaccharide blocks and a linear copolymer may be formed with another preselected moiety, e.g. lactic acid or epsilon.-caprolactone. The resulting polymer includes alginate blocks which permit ionically catalyzed gelling, and oligoester blocks which produce more rapid degradation depending on the

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synthetic design. Alternatively, alginate polymers may be used, wherein the ratio of mannuronic acid to guluronic acid does not produce a firm gel, which are derivatized with hydrophobic, water-labile chains, e.g., oligomers of epsilon-caprolactone. The hydrophobic interactions induce gelation, until they degrade in the body.

Additionally, polysaccharides which gel by exposure to monovalent cations, including bacterial polysaccharides, such as gellan gum, and plant polysaccharides, such as carrageenans, may be crosslinked to form a hydrogel using methods analogous to those available for the crosslinking of alginates described above. Polysaccharides which gel in the presence of monovalent cations form hydrogels upon exposure, for example, to a solution comprising physiological levels of sodium. Hydrogel precursor solutions also may be osmotically adjusted with a nonion, such as mannitol, and then injected to form a gel.

Polysaccharides that are very viscous liquids or are thixotropic, and form a gel over time by the slow evolution of structure, are also useful. For example, hyaluronic acid, which forms an injectable gel with a consistency like a hair gel, may be utilized. Modified hyaluronic acid derivatives are particularly useful. As used herein, the term "modified hyaluronic acids" refers to chemically modified hyaluronic acids. Modified hyaluronic acids may be designed and synthesized with preselected chemical modifications to adjust the rate and degree of crosslinking and biodegradation. For example, modified hyaluronic acids may be designed and synthesized which are esterified with a relatively hydrophobic group such as propionic acid or benzylic acid to render the polymer more hydrophobic and gel-forming, or which are grafted with amines to promote electrostatic self-assembly. Modified hyaluronic acids thus may be synthesized which are injectable, in that they flow under stress, but maintain a gel-like structure when not under stress. Hyaluronic acid and hyaluronic derivatives are available from Genzyme, Cambridge, Mass. and Fidia, Italy.

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Other polymeric hydrogel precursors include polyethylene oxide-polypropylene glycol block copolymers such as PLURONICS or TETRONICS, which are crosslinked by hydrogen bonding and/or by a temperature change, as described in Steinleitner et al., Obstetrics & Gynecology, 77:48-52 (1991); and Steinleitner et al., Fertility and Sterility, 57:305-308 (1992).

Other materials which may be utilized include proteins such as fibrin, collagen and gelatin. Polymer mixtures also may be utilized. For example, a mixture of polyethylene oxide and polyacrylic acid which gels by hydrogen bonding upon mixing may be utilized. In one embodiment, a mixture of a 5% w/w solution of polyacrylic acid with a 5% w/w polyethylene oxide (polyethylene glycol, polyoxyethylene) 100,000 can be combined to form a gel over the course of time, e.g., as quickly as within a few seconds.

Covalently crosslinkable hydrogel precursors also are useful. For example, a water soluble polyamine, such as chitosan, can be cross-linked with a water soluble diisothiocyanate, such as polyethylene glycol diisothiocyanate. The isothiocyanates will react with the amines to form a chemically crosslinked gel. Aldehyde reactions with amines, e.g., with polyethylene glycol dialdehyde also may be utilized. A hydroxylated water soluble polymer also may be utilized.

Alternatively, polymers may be utilized which include substituents which are crosslinked by a radical reaction upon contact with a radical initiator. For example, polymers including ethylenically unsaturated groups which can be photochemically crosslinked may be utilized, as disclosed in WO 93/17669. In this embodiment, water soluble macromers that include at least one water soluble region, a biodegradable region, and at least two free radical-polymerizable regions, are provided. The macromers are polymerized by exposure of the polymerizable regions to free radicals generated, for example, by photosensitive chemicals and or light. Examples of these macromers are PEG-oligolactyl-acrylates, wherein the acrylate groups are polymerized using radical initiating systems, such as an eosin dye, or by brief exposure to

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ultraviolet or visible light. Additionally, water soluble polymers which include cinnamoyl groups which may be photochemically crosslinked may be utilized, as disclosed in Matsuda et al., ASAID Trans., 38:154-157 (1992).

Water soluble polymers with charged side groups may be crosslinked by reacting the polymer with an aqueous solution containing ions of the opposite charge, either cations if the polymer has acidic side groups or anions if the polymer has basic side groups. Examples of cations for crosslinking of the polymers with acidic side groups to form a hydrogel are monovalent cations such as sodium, and multivalent cations such as copper, calcium, aluminum, magnesium, strontium, barium, and tin, and di-, tri- or tetra-functional organic cations such as alkylammonium salts. Aqueous solutions of the salts of these cations are added to the polymers to form soft, highly swollen hydrogels and membranes. The higher the concentration of cation, or the higher the valence, the greater the degree of cross-linking of the polymer. Additionally, the polymers may be crosslinked enzymatically, e.g., fibrin with thrombin.

2. Please add the following paragraphs after page 10, line 12:

Thermoplastic polymers include pharmaceutically compatible polymers that are bioerodible by cellular action, are biodegradable by action of non-living body fluid components, soften when exposed to heat but return to the original state when cooled and are capable of substantially dissolving or dispersing in a water-miscible carrier or solvent to form a solution or dispersion. Upon contact with an aqueous fluid and the dissipation of the solvent component, the thermoplastic polymers are capable of coagulating or solidifying to form a solid or gelatinous matrix suitable for use as an implant in an animal. The kinds of thermoplastic polymers suitable for the present composition generally include any having the foregoing characteristics. Examples are polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides,

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polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein. Polylactides, polycaprolactones, polyglycolides and copolymers thereof are highly preferred thermoplastic polymers.

The thermoplastic polymer is combined with a suitable organic solvent to form a solution. The solubility or miscibility of a polymer in a particular solvent will vary according to factors such as crystallinity, hydrophilicity, capacity for hydrogen-bonding and molecular weight of the polymer. Consequently, the molecular weight and the concentration of the polymer in the solvent are adjusted to achieve desired miscibility. Highly preferred thermoplastic polymers are those which have a low degree of crystallization, a low degree of hydrogen-bonding, low solubility in water, and high solubility in organic solvents.

The composition of the invention may as well be a liquid formulation of a thermosetting oligomeric pre-polymer or copolymer which is capable of cross-linking or hardening to provide a microporous gelatinous or solid matrix suitable for use as an implant in an animal, including a human. The thermosetting pre-polymers and resulting cross-linked polymers and copolymers are biocompatible, and biodegradable and/or bioerodible.

The pre-polymers are preferably low molecular weight polymers or oligomers having end functional groups that are reactive with acryloyl chloride to produce acrylic ester-terminated pre-polymers. Acrylic pre-polymers for use in the compositions may be synthesized according to a variety of methods including, but not limited to, reaction of a carboxylic acid, such as acrylic or methacrylic acid, with an alcohol; reaction of a carboxylic acid ester, such as methyl acrylate or methyl methacrylate, with an alcohol by transesterification; and reaction of an isocyanatoalkyl acrylate, such as isocyanatoethyl methacrylate, with an alcohol.

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The thermosetting prepolymers are also short chain polyol derivatives of the thermoplastic polymers described herein. The polyol terminated derivatives are converted to acrylic ester terminated prepolymers by any suitable method. Examples are short chain polyol derivatives of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein.

A polymer matrix and implant prepared with thermosetting prepolymers is composed of poly(DL-lactide-co-caprolactone) (DL-PLC). To prepare the DL-PLC polymer matrix, DL-lactide or L-lactide and gamma-caprolactone are co-polymerized in the presence of a multifunctional polyol initiator and a curing agent to produce hydroxy-terminated PLC prepolymers. This polyol-terminated pre-polymer is then converted to an acrylic ester-terminated pre-polymer by any suitable method, as for example, by acylation of the alcohol terminus with acryloyl chloride by means of, for example, a Schotten-Baumann technique (reaction of acyl halide with alcohol).

Optionally, a curing agent, such as a catalyst, may be added to the acrylic pre-polymer mixture to enhance cross-linking of the pre-polymers and the subsequent coagulation or solidification of the resulting polymer to form a matrix. For example, the acrylic pre-polymer, in an amount of about 5 grams, may be added to a solution of benzoyl peroxide (BP) in about 1 ml of CH<sub>2</sub>Cl<sub>2</sub>. Optionally, other acrylic monomers may be added to the acrylic pre-polymer mixture before adding the curing agent. The acrylic pre-polymer mixture may be cured in air at room temperature, or in a preheated vacuum oven.

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Preferred catalysts for the preparation of the PLC prepolymers are basic or neutral ester-interchange (transesterification) catalysts, as for example, metallic esters of carboxylic acids containing up to 18 carbon atoms, formic, acetic, lauric, stearic, and benzoic acid. Preferred catalysts include, for example, stannous octoate and stannous chloride.

A multi-functional polyol chain initiator may be included in the thermosetting polymer compositions to vary the molecular weight and composition of the polymer. For example, a bifunctional chain initiator such as ethylene glycol, may be included to produce a bifunctional polymer, or a trifunctional initiator, such as trimethylolpropane, may be used to produce a trifunctional polymer. Further, the molecular weight of the polymer or co-polymer may be varied according to the concentration of the chain initiator in the composition. For example, a high concentration of a bifunctional chain initiator may make available an initiator molecule for each polymer chain, while a low concentration may contain one initiator molecule for every two polymer chains.

Following the addition of the curing agent, the pre-polymer polymer mixture preferably remains in liquid form for a period of time effective to allow administration of the composition to the implant site. Thereafter, the cross-linking reaction preferably continues until a solid or gelatinous polymer matrix is produced. Accordingly, the pre-polymer mixture cures, or solidifies, in situ to form a polymer matrix which is capable of biodegradation and/or bioabsorption over time.